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Pharmacokinetics of *cis*-Diamminedichloroplatinum (II) Given as Low-Dose and High-Dose Infusions

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A pharmacokinetic analysis of *cis*-diamminedichloroplatinum (II) (DDP) was conducted comparing low-dose daily bolus infusions, and high-dose drip infusions. Eight patients with gastric cancer were treated with low-dose daily bolus infusions of DDP to a total daily dose of 75 mg/m^2 bid for 5 days. Four patients with esophageal cancer and one patient with gastric cancer were treated with high-dose drip infusions of DDP to a total daily dose of 70–80 mg/m^2. Side effects were assessed in all the patients, and the platinum concentration in plasma was determined by an atomic absorption method. The peak plasma concentration (C_{max}) and area under the curve (AUC) were calculated in four cases of the low-dose therapy, and three cases of the high-dose therapy. The side effects of DDP were evaluated according to the World Health Organization (WHO) grading, paying particular attention to nausea/vomiting, appetite loss, renal toxicity, and bone marrow suppression. The incidence of nausea/vomiting and appetite loss was significantly reduced with low-dose daily bolus infusions when compared to the high-dose drip infusions. Bone marrow toxicity and renal toxicity were similar with both administration methods, although hydration was required for the high-dose drip infusions to prevent renal toxicity. The peak plasma concentration (C_{max}) of total and free platinum, and the area under the curve (AUC) of total platinum, were similar with both administration methods, while the AUC of free platinum was higher with the low-dose daily bolus infusions compared to the high-dose drip infusions. The time when the concentration of total platinum was >1 μg per ml (holding time) was significantly longer with the high-dose drip infusions than with the low-dose daily bolus infusions. The present study suggests that low-dose daily bolus infusions of DDP would be useful in reducing gastrointestinal toxicity, without reducing the area under the curve which is important for antitumor activity.

KEY WORDS: *cis*-diamminedichloroplatinum(II), low-dose consecutive infusion, pharmacokinetics, area under the curve (AUC), holding time

INTRODUCTION

Gastric cancer remains the leading cause of cancer-related deaths in Japan [1] despite the percentage decrease in mortality. In order to further decrease the mortality due to gastric cancer, potent combination cancer chemotherapy combined with surgery has been investigated. *cis*-diamminedichloroplatinum (II) (cisplatin; DDP) is one of the most effective antitumor agents available for the treatment of a wide variety of malignancies including genitourinary, gynecological, head & neck, esophageal and gastric cancers [2]. The efficacy rate of DDP against

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TABLE I. Background Factors of the Patients

Treatment	Low-dose daily consecutive infusion[a]	High-dose drip infusion[b]
Case used for pharmacokinetic analysis	4	3
Gastric: esophageal	4:0	1:2
Age (average ±SD)	53 ± 11.5	62.3 ± 2.3
Case used for analysis of side effects	8	5
Gastric: esophageal	8:0	1:4
Age (average ±SD)	55.28 ± 12.5	59.6 ± 6.69

[a]Low-dose consecutive infusion of cisplatin at a total dose of 75 mg/m^2 in a schedule of q5d.
[b]High-dose single infusion of cisplatin at a total dose of 70–80 mg/m^2.

gastric cancer has been reported to be in the range 15–25% [3–9], equivalent to conventional agents such as mitomycin C and 5-fluorouracil [10]. However, its side effects which include, nausea/vomiting, appetite loss, renal toxicity and bone marrow suppression, have prevented its wider application in the treatment of gastric cancer. DDP has been administered to patients with gastric cancer as a single intravenous administration. By contrast, in genitourinary [11,12] and head and neck cancers [13,14], DDP has been administered either as a continuous infusion or as a low-dose bolus infusion given on consecutive days. We have reported that the in vitro antitumor activity of DDP against human gastric cancer cell lines, MKN-45 and MKN-74 [15], depended on its time × concentration product (AUCvitro). The in vivo antitumor activity of DDP against the human gastric cancer xenografts, MKN-45, SC-1-NU, SC-9, and St-15, depend on the total dose administered as well as its area under the curve (AUC) [16,17]. In the present study, we investigated the pharmacokinetics of DDP administered as either low-dose daily bolus infusions or high-dose drip infusions, and compared the side effects of the two regimens.

MATERIALS AND METHODS

Drug

cis-Diamminedichloroplatinum(II) (cisplatin: DDP) was purchased from Nippon Kayaku Co., Ltd. (Tokyo).

Patients

Nine patients with gastric cancer and four patients with esophageal cancer took part in the study. All patients gave informed consent. The clinical features of the patients are shown in Table I.

Administration of DDP

In eight patients, DDP was administered intravenously at a dose of 15 mg/m^2 as a bolus infusion one time daily for 5 consecutive days. Five other patients were treated with DDP given intravenously through a drip at a dose of 35–40 mg/m^2, bid.

Pharmacokinetics

Venous blood samples were obtained in heparinized tubes 5, 30, 60, 90, 120, 240, 480, and 1440 min after completing the administration of DDP. The plasma was separated by centrifugation at 3,000 rpm for 10 min. One-half of the plasma was stored for the assay of total platinum at −20°C, and the remaining half was centrifuged again at 3,000 rpm using the membrane of the Centrifree micropartition system (Amicon, Beverly, MA), and stored at −20°C for assay of free platinum. Total and free platinum was detected by atomic absorption spectrophotometry and expressed as μg/ml [18]. The data were fitted to either a one- or two-compartmental model, and either Gauss–Newton, damping Gauss–Newton, or the simplex method was used as the algorithm for calculation [19]. Peak plasma concentration (C_{max}), the AUC of total and free platinum, and the holding time when the concentration of total platinum was more than 1 μg/ml, were calculated in the two groups.

Side Effects of Cisplatin

The side effects of DDP were classified according to the WHO grading. The side effects were expressed as a ratio of the number of cases with a WHO grade of more than two, compared to the total number of evaluable cases.

Statistical Analysis

Statistical analysis was performed by Student's *t*-test.

RESULTS

Pharmacology

The pharmacokinetic parameters of the two groups are summarized in Table II. When 15 mg/m^2 of DDP was administered intravenously, the C_{max} of total and free platinum was 2.68 ± 0.58 and 1.26 ± 0.24 μg/ml, respectively, and the AUC was 104.2 ± 24.2 and 3.4 ± 0.32 μg · hr/ml respectively. When 35–40 mg/m^2 of DDP was administered through an intravenous drip twice a day, the C_{max} of total and free platinum was 3.05 ± 0.47 and 0.86 ± 0.28 μg/ ml, respectively, while the AUC was 150.7 ± 33.7 and

TABLE II. Pharmacokinetics of DDP, Comparing Low-Dose Daily Consecutive Infusion With High-Dose Drip Infusion

Treatment	Low-dose daily consecutive infusion[a]	High-dose drip infusion[b]
Patient number	4	3
Peak plasma concentration (μg/ml)		
Free platinum	1.26 ± 0.24**	0.86 ± 0.28**
Total platinum	2.68 ± 0.58**	3.05 ± 0.47**
Area under the curve (μg · hr/ml)(120h)		
Free platinum	3.4 ± 0.32*	0.62 ± 0.19*
Total platinum	104.2 ± 24.2**	150.7 ± 33.7**

[a]Low-dose consecutive infusion of cisplatin at a total dose of 75 mg/m² in a schedule of q5d.
[b]High-dose single infusion of cisplatin at a total dose of 70–80 mg/m².
*$P < 0.001$.
**N.S., not significant.

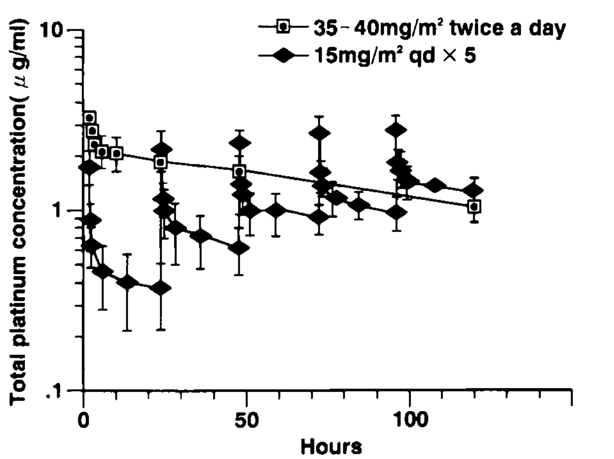

Fig. 1. Change in the level of total platinum in plasma with time. Total platinum was eliminated biphasically in low-dose daily consecutive and high-dose drip infusion.

0.62 ± 0.19 μg · hr/ml, respectively. The C_{max} of total platinum and free platinum was not significantly different with the two methods of administration. Although the AUC of total platinum was also not significantly different with the two methods, the AUC of free platinum was significantly higher with the low-dose daily bolus infusions than with the high-dose drip infusions.

The change in total platinum concentrations in plasma with times is shown in Figure 1 and Table III; total platinum was eliminated biphasically with both administration methods. The C_{max} and AUC rose according to the times of administration with the low-dose daily bolus infusions. The holding time when the total platinum concentration was more than 1.0 μg/ml was higher (107.5 ± 2.7 hr), for the high-dose drip infusions than for the low-dose bolus infusions (47.6 ± 25.6 hr) (Table III).

TABLE III. Time When the Concentration of Total Platinum Was >1.0 μg/ml in Low-Dose Daily Consecutive and High-Dose Drip Infusion

Treatment	Holding time (min)
Low-dose daily consecutive infusion (n = 4)	47.6 ± 25.6*
High-dose drip infusion (n = 3)	107.5 ± 21.7*

*$P < 0.025$, $t = 3.25$.

TABLE IV. Side Effects of Cisplatin, Compared With Low-Dose Daily Consecutive Infusion With High-Dose Drip Infusion

	Treatment	
Side effects	Low-dose daily consecutive infusion[a]	High-dose drip infusion[b]
Patients number	8	5
Nausea/vomiting	0%(0/8)[c,*]	100%(5/5)*
Appetite loss	0%(0/8)*	100%(5/5)*
Renal toxicity	0%(0/8)**	0%(0/5)**
Bone marrow toxicity	12.5%(1/8)**	40%(2/5)**

[a]Low-dose daily consecutive infusion of cisplatin at a total dose of 75 mg/m² in a schedule of q5d.
[b]High-dose drip infusion of cisplatin at a total dose of 70–80 mg/m².
[c]Number of cases over WHO grade 2/number of evaluable cases.
*$P < 0.05$.
**N.S., not significant.

Side Effects

The side effects of DDP with both administration methods are shown in Table IV. Gastrointestinal toxicity was evaluated in terms of nausea/vomiting and appetite loss. No nausea/vomiting and appetite loss were observed in the eight patients who had low-dose daily bolus infusions, while all the patients who had high-dose drip infusions developed the side effects, the difference being statistically significant. Renal toxicity was not observed in either of the groups, although hydration was required in all patients given high-dose infusions. Bone marrow suppression was observed in one of eight patients given the low-dose bolus infusion, and two of the five patients given the high-dose drip infusion, but this was not statistically significant.

DISCUSSION

Although DDP is one of the key drugs used for the treatment of gastric cancer, its side effects, including the gastrointestinal toxicity and renal toxicity have prevented its conventional use [2]. This is partly because the antitumor activity of DDP is thought to be dependent on its maximum concentration in the serum (C_{max}) [20,21]. In fact, Takahashi et al. [22] have reported that the antitumor effect of DDP on G/S human gastric cancer xenografts in nude mice was more potent when a total dose of 9.1 mg/kg was administered as a bolus than when it was administered in divided doses, suggesting that DDP

would be classified as a type Ib dose-dependent agent, according to the criteria of Shimoyama [23]. Low-dose daily administration of DDP has been used for genitourinary [11,12], head and neck [13,14], non-small-cell lung carcinomas [24], and recently, also for gastric cancer [25]. We have reported that the antitumor activity of DDP in vitro depends on its time × concentration product (AUC) [15], while in vivo, it depends on the AUC [16,17]. These results suggest that DDP would be useful administered as small divided doses that would preserve its antitumor activity and reduce its side effects.

Jacobs et al. [14] have reported that the response rate to DDP administered at a dose of 50–130 mg/m^2 over 24 hr for advanced head and neck cancer was equivalent to that obtained by a large bolus infusion, but its toxicity was reduced. Belliveau et al. [26] compared the pharmacokinetics of DDP when administered as a continuous 5-day infusion, and as one 30-min infusion given at a similar dose; they found that the C_{max} of free platinum was 10–40 times lower for the short-term infusion, while the AUC of free platinum was greater with the continuous infusion [26].

In the present study, the incidence of gastrointestinal toxicity, including nausea/vomiting and appetite loss, was significantly reduced with a low-dose bolus infusion, while the C_{max} of total and free platinum, and the AUC of total platinum, were not significantly different with two methods. However, the AUC of free platinum was significantly higher with the low-dose daily bolus infusion than for the high-dose drip infusion. The holding time for platinum concentration of more than 1.0 μg/ml was significantly longer with the high-dose infusion method than with the low-dose method. The longer holding time may thus be one of the reasons why gastrointestinal toxicity is more common with high-dose infusion therapy. Since Holdener et al. [27] have reported that only the free platinum species is cytotoxic to cells, low-dose daily bolus infusions may be useful in preserving the higher AUC of free platinum, while at the same time reducing the gastrointestinal toxicity. Thus, it can be surmised that low-dose bolus infusions will be as effective against carcinomas as the high-dose infusion therapy.

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